REMARKS

Entry of the foregoing, re-examination and reconsideration of the application identified in caption, pursuant to and consistent with 37 C.F.R. §1.116 and in light of the remarks which follow are respectfully requested.

As correctly indicated in the Office Action summary, Claims 45-48, 50-52 and 54-61 are pending. The Office Action Summary also indicates that claims 46-48, 51, 52 and 55-61 are rejected. Applicants note with appreciation that the Office Action Summary further indicates that Claims 45, 50 and 54 are allowed. Thus, Claims 45-48, 50-52 and 54-61 are currently pending in this application.

Applicants further note with appreciation that the Examiner has withdrawn the double patenting rejection of Claims 45-48, 50-52 and 54-61.

I. THE INFORMATION DISCLOSURE STATEMENT

The Office Action states that the IDS filed on June 16, 2003, Paper No. 9, has been "reviewed to the extent each reference was located in the parent application." In this regard, it is noted that the Examiner has not initialed IDS documents Nos. 6, 25, 22, 25, 32 35 and 36 because these documents are not present in the instant file and are missing in the file of the parent application, 09/500,650.

Copies of these documents were previously submitted in prior Application Serial No. 09/500,650, filed February 9, 2000 and/or prior Application Serial No. 09/172,763 filed October 15, 1998, upon which Applicants rely for the benefits provided in 35 U.S.C. § 120. In accordance with 37 C.F.R. § 1.98(d), copies of the listed documents were not

required to be included with the previously filed Information Disclosure Statement. Applicants respectfully submit that such copies may be present in the prior grandparent Application Serial No. 09/172,763 filed October 15, 1998. If such copies still cannot be located in the grandparent case, it is respectfully requested that the Examiner contact the undersigned.

It is respectfully requested that an Examiner-initialed copy of the Form 1449 be returned to the undersigned.

II. THE REJECTION OF CLAIMS 46-48, 51, 52 AND 55-61 UNDER 35 U.S.C. §1.112, first paragraph

Dependent claims 46-48, 51, 52 and 55-61 were rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to practice the invention. Respectfully, Applicants traverse this rejection.

The invention relates generally to novel α-aryl-*N*-alkylnitrones and their use as therapeutic agents, including the treatment and/or prevention of neurological, autoimmune and inflammatory conditions in mammals. *See, e.g.*, page 1, lines 11-15. As explained in the specification, it was known in the art that certain groups of patients were at greater risk for neurological, autoimmune and inflammatory conditions. Indications of a greater propensity to such disease states is detailed in the specification. *See, e.g.*, pages 1-4, 15-16, and the Examples on pages 69-77.

For example, it is well known that patients with Alzheimer's disease develop amyloid plaque deposits around and between the nerve cells of their brain. As stated in the specification, since the deposition of amyloid β-peptide is associated with the development of Alzheimer's disease, compounds which effectively disrupt the formation of Aβ (1-40) beta-pleated sheets are potentially useful for preventing Alzheimer's disease-related amyloid deposits. As explained in the specification, compounds that intervene in Aβ (1-40) or Aβ (1-42) beta-pleated sheet formation can be useful for preventing Alzheimer's disease-related amyloid deposits, and thus for preventing or ameliorating Alzheimer's disease in such a patient.

Similarly, as explained in the specification, compounds are evaluated for their ability to protect against Aβ (25-35)-induced neuronal cell loss in rat embryonic hippocampal neuronal/astrocyte cultures. Compounds that are effective in this *in vitro* test are potentially useful for reducing or preventing neuronal cell loss in patients afflicted with Alzheimer's disease or other neurodegenerative conditions. *See, e.g.*, pages 1-2.

Also, as explained in the specification, another indication that a patient is predisposed to such conditions relates to the observation that β-amyloid increases the release of cytokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNFα) in human monocyte cells induced with lipopolysaccharide (LPS). IL-1β, IL-6 and TNFα are proteins associated with inflammatory and immune responses. As previously mentioned, the deposition of fibrils in the brains of Alzheimer's patients is associated with inflammation of the surrounding support cells. Thus, compounds effective

in this *in vitro* test are potentially useful for reducing and/or preventing the inflammation associated with Alzheimer's disease. In fact, elevated levels of IL-1β, IL-6 and TNFα, as well as other cytokines are associated with a wide variety of inflammatory and autoimmune conditions. Accordingly, compounds that inhibit the production of such cytokines are potentially useful for treating such inflammatory and autoimmune conditions. *See, e.g.*, pages 2-3.

Yet another *in vivo* disease model is based on the observation that certain strains of autoimmune mice develop cognitive deficits as they mature. Thus, compounds that prevent or reduce such cognitive deficits are potentially useful for preventing and/or treating neurodegenerative and autoimmune conditions. *See, e.g.*, pages 3-4.

According to the invention, certain novel α-aryl-*N*-alkylnitrone compounds of this invention effectively inhibit the formation of Aβ(1-42) beta-pleated sheets and/or protect against neuronal cell loss and/or inhibit the release of cytokines, such as IL-1β and TNFα. Additionally, in *in vivo* tests, these componds have been found to reduce the cognitive impairment caused by Aβ(25-35)/ibotenate and to reduce the cognitive deficits that develop in certain strains of autoimmune mice. Accordingly, such compounds are useful for the prevention and/or treatment of neurodegenerative, autoimmune and inflammatory conditions in mammals. *See, e.g.*, page 4 and pages 14-15, as well as the Examples on pages 69-77.

Examples of neurodegenerative disease as set forth in the specification include Alzheimer's disease, Parkinson's disease and HIV dementia. *Please see* page 14.

Examples of autoimmune disease as set forth in the specification include systemic lupus and multiple sclerosis. *Please see* page 15. Examples of inflammatory disease as set forth in the specification include rheumatoid arthritis, septic shock, erythema nodosum leprosy, septicemia, uveitis, adult respiratory distress syndrome, and inflammatory bowel disease. *Please see* pages 14-15. It is noted that each of the independent claims have been allowed, and thus it is only the dependent claims to specific disease states that stand rejected. However, one of ordinary skill in the art would have recognized such disease states as falling within the broad definitions set forth in the independent claims.

Respectfully, when the claimed invention is utilized as disclosed in the application, it can be used in the prevention or amelioration of a neurodegenerative, autoimmune and/or inflammatory disease, in a patient at risk for developing a neurodegenerative, autoimmune and/or inflammatory disease. Such patients would have been identified, according to early signs of the disease, as explained in the specification. By the present amendment, the Claims have been amended to more clearly set forth the invention.

As stated in *Ex parte Forman* (230 USPQ 546 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

As, the Office is aware, "[a] patent need not teach, and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81,

94 (Fed. Cir. 1986). The law does not require a specification to be a blueprint in order to satisfy the requirement for enablement under 35 U.S.C. § 112, first paragraph. Thus, not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be. *Staehelin v. Secher*, 24 U.S.P.Q.2d 1513, 1516 (Bd. Pat. App. & Int. 1992). Applicants submit that the specification provides adequate description of how to use the methods described.

In order to make a rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993) (Examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth. *See* MPEP § 2164.04.

Applicants respectfully submit that the claims are enabled by the specification.

Quantity of experimentation necessary, guidance provided and working examples

Applicants submit that the undue experimentation is not necessary in order for the skilled artisan to practice the methods of the claimed invention. The fact that

experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). *See also In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

To that end, Applicants submit that the specification provides methods of making the compounds now patented in the parent case, methods of using the compounds of the claimed invention, as well as using the claimed methods to treat specific conditions (*see* Examples).

State of the prior art, relative skill of those in that art predictability and unpredictability of the art

With regard to the state of the art, as well as to the level of skill in the art and the predictability of the art, Applicants submit that the skill level in this art is high. Applicants have provided multiple references in the Information Disclosure Statement showing that research and treatment methods are well known. Thus, the skilled artisan would not have difficulty fine tuning the claimed methods if needed. With regard to predictability, Applicants again turn the Examiner's attention to the data and experimentation provided by the Applicant in the Examples.

Thus, Applicants submit that in light of the formulations and methods of using the claimed compounds as provided in the instant specification, the skilled artisan would not

only be able to successfully practice the claimed methods, but would also have an expectation of therapeutic success in treating the claimed conditions.

Finally, Applicants note that although the rejection of Claims 45-48, 50-52 and 54-61 presented in the outstanding Office Action is presented as a rejection under 35 U.S.C. § 112, first paragraph (enablement), the rejection appears to actually be a rejection pursuant to 35 U.S.C. § 101 (utility). Applicants note that a rejection under 35 U.S.C. § 101 would clearly be inappropriate in the present case, as no incredible utility has been set forth for the claimed invention.

Accordingly, for all of the above reasons, Applicants respectfully request withdrawal of this rejection.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such action is earnestly solicited.

If there are any questions concerning this paper or the application in general, the Examiner is invited to telephone the undersigned.

Respectfully submitted,

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By: G Whitney Hapangama

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Limited Recognition Under 37 C.F.R. §10.9(b)
(See Attached Document)

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BEFORE THE OFFICE OF ENROLLMENT AND DISCIPLINE
UNITED STATE PATENT AND TRADEMARK OFFICE

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Expires: May 14, 2004

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